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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *99,100,103-107,109,110,113-117,119 and 121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99, 100, 103-107, 109, 110, 113-117, 119, and 121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 11/30/09 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/29/09 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

Claims 99, 100, 103-107, 109, 110, 113-117, 119, and 121 are pending in the instant application.

Applicant's arguments and/or amendments filed on 11/30/09, with respect to the rejection under 35 U.S.C. 112, 1st paragraph have been fully considered and are persuasive. Therefore, this rejection has been withdrawn. However, the rejection under 35 U.S.C. 103(a) is pending as explained below and upon consideration of the instant claim amendments, a new objection is applied as set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 99, 100, 103-107, 109, 110, 113-117, 119, and 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. (WO 96/40266))(cited and of record on PTO-892 mailed on 5/10/06), in view of Nicklin et al. (WO 98/09633)(cited and of record on PTO-892 mailed on 5/10/06) and Levesque et al. (Molecular Pharmacology, 51, 1997, pages 209-216) (cited and of record on the PTO-892 mailed on 5/1/08).

Nyce et al. teach that antisense oligonucleotides may be administered to the lungs of a patient by any suitable means, but preferably administered by generating an

aerosol comprised of respirable particles, the respirable particles comprised of the antisense compound, which particles the subject inhales (see page 10).

Nyce et al. teach that respirable antisense oligonucleotides can be formulated to be liquid or solid (see page 10). Liquid compositions comprise the antisense compound and sterile, pyrogen free water or saline solution (see page 9, for example). Nyce et al. teach that suitable formulations for delivery include powders (see page 12). Nyce et al. teach that respirable antisense oligonucleotides can be formulated into powders and effectively delivered with a metered dose inhaler. Nyce et al. teach methylphosphonate and phosphorothioate linkages to render respirable antisense oligonucleotides more stable *in vivo* (see page 7).

Nyce et al. teach that particles comprised of antisense compound should be of respirable size that is particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Nyce et al. teach that in general, particles ranging from about .5 to 10 microns in size are respirable (see page 10). Therefore, Nyce et al. teach respirable particles “about 1 to about 5 microns”, as instantly recited. Nyce et al. teach that the antisense oligonucleotides may be of any suitable length, e.g. from about 10 to 60 nucleotides in length (see page 8) and specifically exemplify an 18-mer and a 21-mer (see pages 14 and 15) that is phosphorothioated.

Nyce et al. teach a method of administering the aerosolized antisense oligonucleotides to animals *in vivo* (see page 16, for example) and teach uptake of the

oligonucleotide in the lungs. Nyce et al. teach methods of treating asthma via administering an antisense oligonucleotide to the lung of a subject (see page 3).

Nyce et al. teach that the dosage of the antisense compound administered will depend upon the disease to be treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to the subject, etc. Nyce et al. teaches that a dosage of from about .01, .1, or 1 mg/Kg up to 50, 100, or 150 mg/Kg or more is typically employed to treat a human (see page 11). Nyce et al. teach nebulizers and formation of aerosols for delivery of the compound (see page 12).

Nyce et al. do not teach 2'-O-methoxyethyl or 5-methylcytosine modifications.

Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminooxyalkyl modifications (see pages 2-4). Nicklin et al. teach phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5). Nicklin et al. teach that in certain especially preferred embodiments, all backbone linkages are phosphorothioate linkages. Nicklin et al. teach that preferred bases include at least one 5-methylcytosine. Nicklin et al. teach chimeric configurations having one or more regions of 2'-modified nucleotides, particularly 2'-methoxyethyoxy nucleotides (see page 4). Nicklin et al. teach antisense oligonucleotides that are 20 nucleotides in length (see pages 5-10, for example).

Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect (see summary, page 209).

It would have been obvious to incorporate 2'-O-methoxyethyl modifications, as taught by Nicklin et al. and Levesque et al. and 5-methylcytosine modifications, as taught by Nicklin et al. into the antisense oligonucleotides taught by Nyce et al.

One would have been motivated to incorporate 2'-O-methoxyethyl or 5-methylcytosine modifications into the oligonucleotides of the method of Nyce et al. because Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target. Furthermore, Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect. Since Nyce et al. teach other modifications, such as incorporation of phosphorothioates, in order to render the respirable antisense oligonucleotides more stable *in vivo*, one would have been motivated to incorporate other modifications as well that were also known in the art to enhance oligonucleotide activity, as evidenced by Nicklin et al. and Levesque et al.

With regards to the level/degree of modification, as well as the specific dosage, it would have been prima facie obvious to perform routine optimization to determine the optimal level of modification as well as the optimal dosage, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions

> of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular range used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. It was known in the art to deliver modified antisense compounds via aerosol delivery, each of the modifications were known to enhance the delivery of antisense compounds, and the instant doses are within the dosing ranges set forth by Nyce, wherein Nyce teaches the considerations of dosing for optimization.

The instant claims require various broad quantities of each type of modification. It was known in the art at the time the invention was made to deliver oligonucleotides to the lung of mammals via introducing aerosolized oligonucleotides of the instantly recited size range and particle size range that are modified, as taught by Nyce et al. The only difference between the instantly recited method and the method of Nyce et al. is the specific types of chemical modifications, wherein each of the instantly recited chemical modifications were known in the art to benefit the stability of antisense oligonucleotides, as evidenced by Nyce et al., Levesque et al., and Nicklin et al. It is within the realm of routine optimization to incorporate various quantities of the known chemical modifications, as it was known in the art to incorporate the chemical modifications into chimeric configurations, as evidenced by Nicklin et al. Additionally, Levesque et al. specifically teaches successful target inhibition when utilizing a 20-mer antisense

oligonucleotide with phosphorothioates and 2'-methoxyethyls. Therefore, it would have been obvious to try to the instantly recited combination of modifications at different levels/quantities in view of the teachings of Nicklin et al., Levesque et al. and Nyce et al.

Finally, one would have a reasonable expectation of success that the chemical modifications taught by Nicklin et al. and Levesque et al. would benefit the antisense oligonucleotides of Nyce et al. because each of the instantly recited modifications were known in the art at the time the invention was made to enhance the activity of antisense oligonucleotides, as evidenced by Nicklin et al., Levesque et al. and Nyce et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant argues that Nicklin discloses one especially preferred embodiment that does not contain 2'-modified nucleotides. Every embodiment of Nicklin is not required to contain 2'-modified nucleotides to render incorporation of such nucleotides obvious, especially given that Nicklin specifically teaches incorporation of 2'-modified nucleotides and the benefits thereof. Furthermore, the paragraph directly following the passage cited by applicant on page 4 refers to another especially preferred embodiment that does comprise 2'-modified nucleotides.

It is noted that the instant claims are not directed to any specific static pattern of modification, but rather encompass a large genus of possible modification patterns. For

example, the oligonucleotide has at least one phosphorothioate, at least one 2'-O-methoxyethyl, and every cytosine is a 5-methylcytosine. Therefore, the modification pattern embraces a huge genus of possible combinations of quantities of phosphorothioate and 2'-O-methoxyethyl modifications, varying from one of each minimum to every position of each maximum, and every possible combination in between, combined with 5-methylcytosine modification that varies in quantity and position depending upon the target sequence.

Therefore, it is the instant genus that is considered obvious in view of the teachings of the prior art, given that the prior art teaches the benefits of each of the instant modifications, teaches different combinations of the instant modifications, and teaches to deliver oligonucleotides to the lung of mammals via introducing aerosolized oligonucleotides of the instantly recited size range and particle size range that are modified, as taught by Nyce et al. The only difference between the instantly recited method and the method of Nyce et al. is the specific types of chemical modifications, wherein each of the instantly recited chemical modifications were known in the art to benefit the stability of antisense oligonucleotides, as evidenced by Nyce et al., Levesque et al., and Nicklin et al. It is within the realm of routine optimization to incorporate various quantities of the known chemical modifications, as it was known in the art to incorporate the chemical modifications into chimeric configurations, as evidenced by Nicklin et al. Additionally, Levesque et al. specifically teaches successful target inhibition when utilizing a 20-mer antisense oligonucleotide with phosphorothioates and 2'-methoxyethyls. Therefore, it would have been obvious to try

to the instantly recited combination of modifications at different levels/quantities in view of the teachings of Nicklin et al., Levesque et al. and Nyce et al.

Applicant asserts that the instantly claimed method provides unexpected results and compares ISIS 15163 and ISIS 17009 to support such an assertion. It is noted that improved cellular uptake is not a requirement of the instant claims, but rather uptake is required by the claims. There is no reason to expect that combining the modifications that are taught to enhance stability (and wherein Nicklin teaches that chemical modifications enhance uptake) would not result in some level of uptake when incorporated into the method of Nyce. If applicant questions that the combination of these modifications would result in uptake, enablement of the instant claims is in question.

Therefore, it is not unexpected for oligonucleotides with the instant combination of modifications to result in uptake. In order to demonstrate that such a property is unexpected, applicant would need to point to some teaching that sets forth that this combination would likely not result in uptake, which clearly is not the case given that the art teaches the benefits of each of the instant modifications.

Furthermore, the specific oligonucleotides that applicant points to for unexpected results are not commensurate in scope with the instant claims. The example pointed to by applicant is comparing one specific oligonucleotide sequence (therefore does not consider different levels of cytosine modification based upon target sequence), wherein ISIS 15163 has (6) a phosphodiester backbone, 5-methylcytosine modifications based upon the example target sequence, and is modified with 2'-O-methoxyethyls; and ISIS

17009 is phosphorothioated. The instant claims require a combination of all three of these types of modifications and thus the example pointed to by applicant is not representative of the instant genus. Applicant is relying upon one example within a huge genus of molecules, wherein even the single example is not representative of the instantly claimed oligonucleotide within the instant method.

With regards to the teaching of Nicklin regarding increased uptake into cells, Nicklin is clearly referring to the modifications taught by Nicklin. Furthermore, there is no reason to expect that the combinations of modifications taught by Nicklin would not result in cellular uptake given the benefits taught by Nicklin in incorporating such modifications.

Regarding the opinion declaration by Dr. Richard Geary, the declaration does not set forth any reason why one would not expect for the combinations of modifications to result in cellular uptake, which is the instantly recited intended outcome. The statement concentrates on improved cellular uptake, which is not an element of the instant claims and does not set forth what the improvement is in comparison to. The declaration does not set forth any reasoning why combining the modifications of the prior art for the benefits set forth by the prior art would not result in uptake into cells, particularly given that Nyce teaches aerosol administration of modified oligonucleotides and therefore the instant rejection is only based upon incorporating the instant types of modifications. There is clearly motivation in the prior art to combine modifications, including the instant types of chemical modifications, wherein clearly the desire is to reach a target cell via the combination of chemical modification and aerosol delivery.

New Claim Objections

Claims 107 and 117 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 100 and 110, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571) 272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Examiner
Art Unit 1635

/AMY BOWMAN/
Primary Examiner, Art Unit 1635